Amendment under PCT Art. 34

AMENDMENT

To: Commissioner of the Patent Office

1. Identification of the International Application
PCT/JP01/00271

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4. Document to Be Amended
Description and Claims

5. Contents of Amendment
As shown in attached paper:

(1) After "alkylene or alkenylene group" in the description, page 4, line 12, and page 7, line 21, --, with the proviso that the case in which M is a single bond and a hydroxyl group and a phenyl group are simultaneously bonded as substituents to those carbons of A that are bonded to M is

excluded-- is added.

(2) After "imidazole ring" in the description, page 4, line 35, and page 10, line 18, --and an unsubstituted pyridine ring-- is added.

(3) "a pyridyl group," in the description, page 10, line 25, is deleted.

(4) "cation salt" in the description, page 73, line 12, is changed to read --salt--.

(5) Before "alkali metal ions" and "organic bases" in the description, page 73, lines 13 and 15, --salts of-- is added, respectively.

(6) After "glucamine" in the description, page 73, line 20, --salts of-- is added.

(7) "benzoic acid derivative" in the description, page 74, lines 22 - 23, 29 and 31, is changed to read --benzimidazole derivative of the present invention--.

(8) "the obtained" in the description, page 77, line 27, is deleted.

(9) "Production of Compound No. 743" in the description, page 103, line 9, is changed to read --Production of 5-(1-((1,4-dimethylindole-3-yl)methyl) benzimidazole-2-yl)pentanoic acid--.

(10) After "alkylene or alkenylene group" in claim 1, page 117, line 2, --, with the proviso that the case in which M is a single bond and a hydroxyl group and a phenyl group are simultaneously bonded as substituents to those carbons of

A that are bonded to M is excluded-- is added.

(11) After "imidazole ring" in claim 1, page 117, line 27, --and an unsubstituted pyridine ring-- is added.

6. List of Attached Documents

(1) Description

pages 4, 4/1, 7, 7/1, 10, 10/1, 73, 74, 74/1, 77 and 103

(2) Claims

Pages 117 and 117/1

case in which the alkyl portions of geminal two alkoxy groups are connected to form a ring), a linear or branched alkylthio group having 1-6 carbon atoms, a linear or branched alkylsulfonyl group having 1-6 carbon atoms, a linear or branched acyl group having 1-6 carbon atoms, a linear or branched acylamino group having 1-6 carbon atoms, a trihalomethyl group, a trihalomethoxy group, a phenyl group, an oxo group, and a phenoxy group that may be substituted by one or more halogen atoms; and, one or more of these substituents may each independently be bonded to optional positions of the alkylene or alkenylene group, with the proviso that the case in which M is a single bond and a hydroxyl group and a phenyl group are simultaneously bonded as substituents to those carbons of A that are bonded to M is excluded;

E represents a $-COOR^3$, $-SO_3R^3$, $-CONHR^3$, $-SO_2NHR^3$, tetrazole-5-yl group, a 5-oxo-1,2,4-oxadiazole-3-yl group or a 5-oxo-1,2,4-thiadiazole-3-yl group (where R^3 is as defined above);

G represents a substituted or unsubstituted, linear or branched alkylene group having 1-6 carbon atoms which may be interrupted by one or more of -O-, -S-, $-SO_2-$ and $-NR^3-$ (where, R^3 is as defined above. Where these atoms or atomic groups exist, they are not bonded directly to the benzimidazole ring.); and, the substituent that can be possessed by said alkylene group is selected from a halogen atom, a hydroxyl group, a nitro group, a cyano group, a linear or branched alkyl group having 1-6 carbon atoms, a linear or branched alkoxy group having 1-6 carbon atoms (including the case in which two adjacent groups form an acetal bond), a trihalomethyl group, a trihalomethoxy group, a phenyl group, and an oxo group;

M represents a single bond or $-S(O)_m-$, where m is an integer of 0-2;

J represents a substituted or unsubstituted heterocyclic group having 4-10 carbon atoms and containing one or more hetero atoms selected from the

group consisting of an oxygen atom, a nitrogen atom and a sulfur atom on its ring, with the proviso that an imidazole ring and an unsubstituted pyridine ring are excluded; the substituent that can be

propylene groups or n- or t-butylene groups. More specific examples include $-CH_2OCH_2-$, $-CH_2OCH_2CH_2-$, $-CH_2SCH_2-$, $-CH_2SCH_2CH_2-$, $-CH_2SO_2CH_2-$, $-CH_2SO_2CH_2CH_2-$, $-CH_2NR^4CH_2-$ and $-CH_2NR^4CH_2CH_2-$. Preferable examples include $-CH_2OCH_2-$, $-CH_2SCH_2-$ and $-CH_2SO_2CH_2-$.

The substituent groups that can be possessed by said alkylene group is selected from a halogen atom, a hydroxyl group, a nitro group, a cyano group, a linear or branched alkyl group having 1-6 carbon atoms, a linear or branched alkoxy group having 1-6 carbon atoms (including the case in which two adjacent groups form an acetal bond), a linear or branched alkylthio group having 1-6 carbon atoms, a linear or branched alkylsulfonyl group having 1-6 carbon atoms, linear or branched acyl group having 1-6 carbon atoms, a linear or branched acylamino group having 1-6 carbon atoms, a trihalomethyl group, a trihalomethoxy group, a phenyl group, an oxo group, and a phenoxy group that may be substituted by one or more halogen atoms. One or more of these substituents may each be independently bonded to optional positions of the alkylene group or alkenylene group, with the proviso that the case in which M is a single bond and a hydroxyl group and a phenyl group are simultaneously bonded as substituents to those carbons of A that are bonded to M is excluded.

Examples of the halogen atom include a fluorine atom, a chlorine atom, a bromine atom and an iodine atom. Preferable examples are a fluorine atom and a chlorine atom.

Specific examples of the linear or branched alkyl group having 1-6 carbon atoms include a methyl group, an ethyl group, an n- or i-propyl group and an n-, i-, s- or t-butyl group, while preferable examples are a methyl group and an ethyl group. A more preferable example is a methyl group.

Specific examples of the linear or branched alkoxy group having 1-6 carbon atoms include a methoxy group, an

ethoxy group, an n- or i-propoxy group and an n-, i-, s- or t-butoxy group, while preferable examples are a methoxy group and an ethoxy group. A more preferable example is a methoxy group.

phenyl group and an oxo group. Specific examples of G include $-CH_2-$, $-CH_2CH_2-$, $-CH_2CO-$, $-CH_2CH_2O-$, $-CH_2CONH-$, $-CO-$, $-SO_2-$, $-CH_2SO_2-$, $-CH_2S-$ and $-CH_2CH_2S-$, while preferable examples are $-CH_2-$, $-CH_2CH_2-$, $-CH_2CO-$ and $-CH_2CH_2O-$. More preferable examples are $-CH_2-$ and $-CH_2CH_2-$, and a particularly preferable example is $-CH_2-$. These groups are bonded on the left hand side to position 1 (N atom) of the benzimidazole ring, while on the right hand side to J.

M represents a single bond or $-S(O)_m-$, where m represents an integer of 0-2. Preferable examples of M are -S- and $-SO_2-$. A particularly preferable example is -S-.

J represents a substituted or unsubstituted heterocyclic group having 4-10 carbon atoms and containing one or more hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom on its ring. However, an imidazole ring and an unsubstituted pyridine ring are excluded. In addition, J is limited to that which can be chemically synthesized.

Specific examples of the unsubstituted heterocyclic groups having 4-10 carbon atoms and containing one or more hetero atoms on its ring selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom include a furyl group, a thienyl group, a thiazolyl group, a pyrimidinyl group, an oxazolyl group, an isooxazolyl group, a benzofuryl group, a benzimidazolyl group, a quinolyl group, an isoquinolyl group, a quinoxalinyl group, a benzoxadiazolyl group, a benzothiaziazolyl group, an indolyl group, a benzothiazolyl group, a benzothienyl group and a benzoisooxazolyl group. A preferable example is a bicyclic heterocyclic ring. More preferable examples are a benzofuryl group, a benzoimidazolyl group, a quinolyl group, an isoquinolyl group, a quinoxalinyl group, a benzoxadiazolyl group, a benzothiazolyl group, an indolyl

group, a benzothiazolyl group, a benzothienyl group and a

dimethylamine solution.

In addition, the indole derivative can be synthesized by referring to the literature of Heterocycles, Vol. 22, No. 1, 195, (1984).

Moreover, benzothiophene, indole and other heterocyclic halides and quaternary salts can be synthesized by referring to other references in the literature such as Heterocyclic Compound Chemistry, (Kondansha Scientific, H. Yamanaka, ed.).

Benzimidazole derivative of the present invention can also be converted to a medically acceptable, non-toxic salt as necessary. Examples of such salts include salts of alkali metal ions such as Na^+ and K^+, alkaline earth metal ions such as Mg^{2+} and Ca^{2+} and metal ions such as Al^{3+} and Zn^{2+}, as well as salts of organic bases such as ammonia, triethylamine, ethylenediamine, propanediamine, pyrrolidine, piperidine, piperazine, pyridine, lysine, choline, ethanolamine, N,N-dimethylethanolamine, 4-hydroxypiperidine, glucosamine and N-methylglucamine. In particular, salts of Na^+, K^+, Ca^{2+}, lysine, choline, N,N-dimethylethanolamine and N-methylglucamine are preferable.

Benzimidazole derivative of the present invention strongly inhibits human chymase activity. More specifically, IC_{50} is 1000 nM or less, preferably 0.01 nM or more to less than 1000 nM, and more preferably 0.05 nM or more to less than 500 nM. The benzimidazole derivative of the present invention having such superior human chymase inhibitory activity can be used as a preventive agent and/or therapeutic agent clinically applicable to various diseases.

Benzimidazole derivative of the present invention can be administered orally or non-orally as a pharmaceutical composition together with a pharmaceutically allowed carrier by forming said pharmaceutical composition into various drug forms. Examples of non-oral administration include intravenous,

subcutaneous, intramuscular, transcutaneous, rectal, nasal and intraocular administration.

Examples of drug forms of said pharmaceutical composition include tablets, pills, granules, powders, liquids, suspensions, syrups and capsules in the case of oral preparations.

Here, for the method of forming tablets, tablets can be formed by an ordinary method using a pharmaceutically acceptable carrier such as a vehicle, binder or disintegration agent. Pills, granules and powders can be formed by an ordinary method using a vehicle and so forth in the same manner as tablets. Liquids, suspensions and syrups can be formed according to an ordinary method using glycerin esters, alcohols, water or vegetable oil. Capsules can be formed by filling granules, powders or liquids and so forth into capsules made of gelatin and so forth.

Non-oral preparations can be administered in the form of an injection preparation in the case of administration by intravenous, subcutaneous or intramuscular administration. Examples of injection preparations include the case in which a benzimidazole derivative of the present invention is dissolved in a water-soluble liquid agent such as physiological saline, or the case in which it is dissolved in a non-aqueous liquid agent composed of an organic ester such as vegetable oil.

In the case of percutaneous administration, a drug form such as an ointment or cream can be used. Ointments can be formed by mixing a benzimidazole derivative of the present invention with an oil or Vaseline and so forth, while creams can be formed by mixing a benzimidazole derivative of the present invention with an emulsifier.

In the case of rectal administration, administration can be performed in the form of a suppository using gelatin soft capsules and so forth.

In the case of nasal administration, a preparation

can be used that is composed of a liquid or powder composition. Examples of bases of liquid preparations

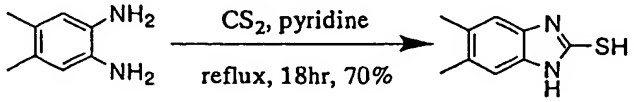
and osteoarthritis.

Examples

The following provides a detailed explanation of the present invention according to its production examples, examples and test examples. However, the scope of the present invention is not restricted in any sense by these examples.

[Reference Example 1]

Production of 5,6-dimethylbenzimidazole-2-thiol

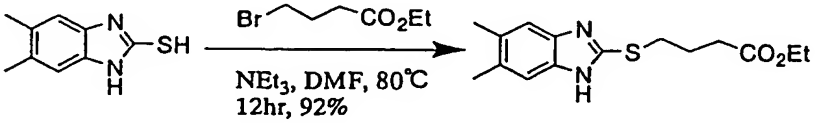


40 ml (0.66 mmol) of carbon disulfide were added to a pyridine solution (40 ml) of 4.5 g (33 mmol) of 5,6-dimethylorthophenylenediamine. After stirring the resulting solution for 18 hours while refluxing under heating, water was added followed by extraction with ethyl acetate. After drying the ethyl acetate phase with anhydrous magnesium sulfate, it was concentrated under reduced pressure and dried for 6 hours at 80°C under reduced pressure to obtain 4.1 g of the target compound (yield: 70%).

^{1}H-NMR (270 MHz, DMSO-d^6) (ppm): 12.30 (br,1H), 6.91 (s,2H), 2.21 (s,6H)

[Reference Example 2]

Production of 4-(5,6-dimethylbenzimidazole-2-ylthio)butanoate ethyl ester



35 µl (0.25 mmol) of triethylamine and 36 µl (0.25 mmol) of 4-bromobutanoate ethyl ester were added to 36 mg (0.20 mmol) of 5,6-dimethylbenzimidazole-2-thiol. After stirring the resulting solution for 12 hours at 80°C, water was added followed by extraction

The solvent was then distilled off under reduced pressure to obtain 16 mg (0.042 mmol) of the target compound (yield: 25%).

Confirmation of the compound was carried out by identifying from the molecular weight using LC-MS.

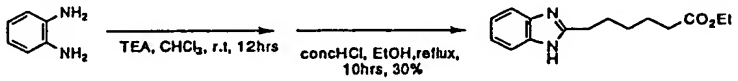
Calculated value M = 379.14, Measured value $(M+H)^+$ = 380.2

[Example 8]

Production of 5-(1-((1,4-dimethylindole-3-yl)methyl)benzimidazole-2-yl)pentanoic acid

Step 1

Production of 5-(benzimidazole-2-yl)pentanoate ethyl ester



696 μl (5.0 mmol) of triethylamine and 893 mg (5.0 mmol) of methyladipochloride were dropped into 10 ml of a chloroform solution containing 540 mg (5.0 mmol) of orthophenylenediamine followed by stirring for 12 hours at room temperature. 20 ml of ethanol and 4 ml of concentrated hydrochloric acid were then added followed by stirring for 10 hours while heating and refluxing. The reaction solution was then neutralized using 5 M aqueous sodium hydroxide solution followed by extraction with ethyl acetate. After washing with water and concentrating under reduced pressure, the residue was purified by silica gel column chromatography (ethyl acetate only) to obtain 359 mg of 5-(benzimidazole-2-yl)pentanoate ethyl ester (yield: 30%).

Step 2

Production of 5-(1-((1,4-dimethylindole-3-yl)methyl)benzimidazole-2-yl)pentanoic acid

substituents may be each independently be bonded to optional positions of the alkylene or alkenylene group, with the proviso that the case in which M is a single bond and a hydroxyl group and a phenyl group are simultaneously bonded as substituents to those carbons of A that are bonded to M is excluded;

E represents a $-COOR^3$, a $-SO_3R^3$, a $-CONHR^3$, a $-SO_2NHR^3$, a tetrazole-5-yl group, a 5-oxo-1,2,4-oxadiazole-3-yl group or a 5-oxo-1,2,4-thiadiazole-3-yl group (where R^3 is as defined above);

G represents a substituted or unsubstituted, linear or branched alkylene group having 1-6 carbon atoms which may be interrupted by one or more of -O-, -S-, $-SO_2-$ and $-NR^3-$ (where, R^3 is as defined above. Where these atoms or atomic groups exist, they are not bonded directly to the benzimidazole ring.); and, the substituent that can be possessed by said alkylene group is selected from a halogen atom, a hydroxyl group, a nitro group, a cyano group, a linear or branched alkyl group having 1-6 carbon atoms, a linear or branched alkoxy group having 1-6 carbon atoms (including the case in which two adjacent groups form an acetal bond), a trihalomethyl group, a trihalomethoxy group, a phenyl group, an oxo group;

M represents a single bond or $-S(O)_m-$, where m is an integer of 0-2;

J represents a substituted or unsubstituted heterocyclic group having 4-10 carbon atoms and containing one or more hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom on its ring, with the proviso that an imidazole ring and an unsubstituted pyridine ring are excluded; the substituent that can be possessed by said heteroaryl group is selected from a halogen atom, a hydroxyl group, a nitro group, a cyano group, a linear or branched alkyl group having 1-6 carbon atoms, a linear or branched alkoxy group having 1-6 carbon atoms (including the case in which two adjacent groups form an acetal

bond), a linear or branched alkylthio group having 1-6 carbon atoms, a linear or branched alkylsulfonyl group having 1-6 carbon atoms, a linear or branched acyl group having 1-6 carbon atoms, a linear or branched acylamino group having 1-6 carbon